

U.S.S.N. 09/506,988

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(isosteres) that mimic the scissile bond normally cleaved by the core structure of aspartyl proteases. These inhibitors are designed and constructed based on a well known correlation between the structure and mechanism of action of the well known aspartic protease family of enzymes. An isostere represents a specific arrangement of atoms that mimic the substrate peptide bond that is normally cleaved by the catalytic core of the targeted protease. In order to "present" the peptide bond *mimic* (the isostere) to the protease, the inhibitor binds the protease and the isostere must "fit" into the catalytic core of the protease.

As discussed repeatedly throughout the specification, isoster inhibitors of aspartic acid proteases are well known, well characterized, and widely tested in patients. See page 3, line 6-page 4, line 8; Figures 1a-1d; see also page 9, line 14-page 10, line 4. There are numerous disclosures of such inhibitors in the scientific literature as well as patents – see, for example, U.S. Patent Nos. 6,121,417 and 5,587,514.

The invention is not the discovery that one can make an inhibitor to an aspartic acid protease by inserting an isoster into the compound, but that one can insert two isosters and the compound will still bind and be able to inhibit. It was not predictable that one could do this; it was equally predictable that one would create instability and decrease binding affinity to the point that the inhibitor would be useless. Binding affinity is critical to efficacy. See, for example, the discussion on page 11, at lines 1-24.

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Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-4, 6-10, and 12 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

With regard to the amount of direction provided by the inventor, the applicant respectfully points out that the transition state isostere described at page 3, line 26 is merely a statement that characterizes a hydroxyethylene group mimicking the transition state of catalysis of an aspartic protease. This is an EXAMPLE of a transition state isostere. There are many other types of transition state isosteres directed to aspartic proteases, as taught at page 4, lines 5-8. However, "*in all cases....a single transition-state isostere is used in an inhibitor since it mimics a substrate peptide with a single hydrolysis site*" (emphasis added). With further reference to the *level of predictability* in the art, the applicant asserts that the central issues are:

- 1) whether one of ordinary skill in the art could design transition state isosteres based upon a well characterized target protease,
- 2) whether one of ordinary skill in the art could "link" together two or more of the designed isosteres in the form of an aspartic protease inhibitor, and
- 3) whether one of ordinary skill in the art could actually inhibit aspartic proteases using these multi-isostere compounds.

With reference to the above-identified point 1, transition state isosteres directed to the active pocket of aspartic proteases (for example, hydroxyethylene, dihydroxyethylene, hydroxyethylamine, phosphinate and reduced amide), are well known and exemplified in the

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specification, as pointed out by the Examiner on page 3 of the Office Action mailed on October 31, 2002. The heretofore identified isosteres were designed to "fit" into the well characterized enzymatic pocket of aspartic proteases. Aspartyl proteases retain a structurally and functionally conserved active pocket (thus defining this class of proteases); the applicant cannot stress this point enough (see, for example, page 3, line 29 to page 4, line 3, of the specification). Isosteric inhibitors are designed based upon this essential information. In view of the foregoing discussion, one of ordinary skill in the art will readily realize that aspartyl protease inhibitors retain similar structural and physical properties because of their stereospecificity for a class of proteases with conserved active pockets to which they bind (the structural/physical characteristics to be designed into the isostere of the inhibitor are predicated on the enzymatic core – which is well-defined and characterized for the claimed class of aspartyl proteases).

With reference to the above-identified point 2, Example 1 and Figure III describe in detail and outline, respectively, the procedure for synthesizing a two isostere aspartyl protease inhibitor, HIV protease inhibitor UIC-98-056. The claimed compositions are directed to protease inhibitors comprising *two or more transition-state isosteres in the polypeptide backbone*. The Applicant respectfully submits that the examiner's assertion that enablement is limited to a particular scope (i.e. only those isosteres that are provided as *examples* in the specification) is inappropriate in view of the many commercially available computer programs that allow for structure analysis of ligands in connection to well structurally characterized targets. The applicant has repeatedly argued that isostere structure is clearly limited based upon its requirement to bind in the core of the aspartyl protease. Page 12 of the specification briefly

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reviews the "origins" of many aspartic proteases. These proteases belong to the "aspartyl" class because of one readily identifiable characteristic: the well-defined structural features of the enzymatic core. Therefore, the combination of these structural features, readily available "structure analysis" computer programs, the example provided in the specification that details the synthesis of one example of a two isostere inhibitor, and the skill level of one in the art, absolutely provides direction to seek other active compounds that are not explicitly a part of the *examples* described in the specification.

The applicant has provided many *examples* of inhibitory isosteres which all share a common feature: their structures are predicated by the target(s) structure/sequence they bind (i.e. hydroxyethylene, dihydroxyethylene, hydroxyethylamine, phosphinate, reduced amide; and other examples are provided in "Vacca" (page 12, lines 22-25; Vacca, "Design of Tight-Binding Human ImmunodeficiencyVirus Type 1 Protease Inhibitors", *Methods in Enzymology*, 241, 313-333; 1994).

With reference to the above-identified point 3, compounds are considered to be active based upon data derived from well-defined assays; assays that are well-known to one of ordinary skill in the art and have been utilized in the art for many, many years. While it has been well-established that the applicant need not provide, in the specification, those methods, assays and reagents that are commonly used and well-known in the art; the applicant did, however, provide clinical resistance studies of 15 mutation sites on HIVPr (Table I) which account for the resistance of 3 identified protease inhibitor drugs, as well as data (K_i values and the ratios between the inhibition constant of the mutants, $K_{i,mut}$, to the inhibition constant of the wild-type

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HIVPr taken as 1.0 – including UIC-98-056) derived from clinical trials (the applicant respectfully directs the examiner's attention to lines 23-21, bridging pages 16 and 17 of the specification). These studies, and those provided in the references (cited within the specification; see, for example, lines 23-21, bridging pages 16 and 17) clearly demonstrate assays which are commonly utilized to determine inhibition of protease activity, as well as an ability to withstand protease resistance. Therefore, the ability of one of ordinary skill in the art to determine a compound's ability to inhibit and resist mutation within a target using nothing more than routine *in vitro* and clinical assays, in combination with the direction provided in the specification (as described above) necessary to elucidate and produce active compounds as claimed, clearly addresses the relevant issues raised by the examiner (nature of the invention, state of the prior art, level of predictability, and the amount of direction; see page 3 of the office action mailed on October 31, 2002).

Claims 1-4, 6-10 and 12 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The applicant respectfully points out that the transition state isostere described at page 3, line 26 is merely a statement that characterizes a hydroxyethylene group mimicking the transition state of catalysis of an aspartic protease. This is an **EXAMPLE** of a transition state

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isostere. There are many other types of transition state isosteres directed to aspartic proteases, as taught at page 4, lines 5-8. However, "***in all cases....a single transition-state isostere is used in an inhibitor since it mimics a substrate peptide with a single hydrolysis site***" (emphasis added; see page 4, lines 5-8). As will be further described below, this form of mimicry (i.e. replacing the scissile bond of the substrate with a non-hydrolysable TS analog that mimics what is normally hydrolyzed by the protease), is *the* definition of a transition state analog.

It is well established that the one of the most common ways in which new molecules are designed involves the use of *known targets as starting points*. Well characterized targets allow for the proposed ligands to be evaluated in the binding site prior to synthesis. Indeed the most potent inhibitors of HIV-1 protease are peptidomimetics and are based on the transition-state (TS) mimic concept. This is very much state-of-the-art in pharmaceutical design involving a medicinal chemist designing inhibitors based on the optimal substrate. As described in the specification, the strategy involves replacing the scissile bond of the substrate with a non-hydrolysable TS analog that mimics this bond. The realization that HIV-1 protease belonged to the aspartic acid class of proteases has led many researchers to screen inhibitors of other aspartyl proteases (e.g. renin and pepsin). Such TS isosteres (already known from previous pepsin/renin work) mimic the tetrahedral intermediate formed in hydrolysis of the peptide.

In essence once a suitable TS mimic is found, amino acid residues in the optimal substrate are deleted/substituted with other moieties to find the optimal inhibitor. This uses both molecular modeling and structure determination (X-ray/NMR). *Much of the literature that claims to use structure-based drug design methods, model a candidate drug by placing it into*

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the active site using a previously determined structure with the same TS mimic. The TS mimic part of the drug is used to position the ligand. The other groups are then built in manually (using computer graphics). An evaluation of the quality of the candidate usually includes steric fit, hydrophobic and hydrogen bond interactions, and/or a highly favorable molecular mechanics energy (inter and intramolecular ligand energy), all of which can be determined by one of ordinary skill in the art. Suitable likely candidates are thus identified. These compounds are then tested for (1) binding affinity and if this proves promising, for (2) bioavailability and, again if this proves promising, (3) a structure would be determined. Successive rounds of such optimization allows one of ordinary skill to combine the characteristics of high affinity (as measured by IC50) and bioavailability (in animal tests). It should be noted that transition-state mimics and robust methods of lead modification have been, and continue to be, the mainstay of modern structure-based drug design.

Rejection Under 35 U.S.C. § 102

Claims 1-4, 6-10, and 12 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent Nos. 5,491,149 and 5,683,999 to Jadhav *et al.* ("Jadhav 1" and "Jadhav 2", respectively). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Jadhav 1

Jadhav 1 teaches substituted dihydroxypropylamines, and derivatives thereof. The compounds taught by Jadhav decrease HIV viral yield and decrease multiplicity of the virus in

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human T-cells *in vitro*. Jadhav 1 fails to contemplate two or more transition state isosteres in a polypeptide backbone, which have *different orientations* (see, for example, page 4, lines 31-32) that mimic the transition state of the aspartic acid protease. It should be noted that these different orientations are critical to stability, binding affinity, and efficacy with regard to protease inhibition and protease resistance mechanisms (see, for example, page 10, lines 10-20).

Jadhav 2

Jadhav 2 is directed to substituted cyclic urea compounds and derivatives thereof. The compounds of Jadhav 2 are taught as inhibiting HIV protease and thereby inhibiting HIV replication. Jadhav 2 fails to contemplate two or more transition state isosteres in a polypeptide backbone, which have *different orientations* (see, for example, page 4, lines 31-32) that mimic the transition state of the aspartic acid protease. It should be noted that these different orientations are critical to stability, binding affinity, and efficacy with regard to protease inhibition and protease resistance mechanisms (see, for example, page 10, lines 10-20).

Summary

The applicant respectfully submits that when anticipation is based on inherency of limitations not expressly disclosed in the asserted anticipating reference, it must be shown that the undisclosed information was known to be present in the subject matter of the reference. *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749-50 (Fed. Cir. 1991). In this case, neither of Jadhav 1 or Jadhav 2 contemplate protease inhibition and combating protease resistance mechanisms as a result of utilizing different orientations of isosteres in an inhibitory compound. Inherency cannot be based on the knowledge of the

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inventor; facts asserted to be inherent in the prior art must be shown by evidence from the prior art. *Cf. In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). The applicant further asserts that only in hindsight of the present application could one realize the nexus between protease inhibition and combating protease resistance mechanisms, and the utilization of two or more isosteres, each oriented differently.

Allowance of claims 1, 2 and 4-8 and 10-12 is respectfully solicited.

Respectfully submitted,



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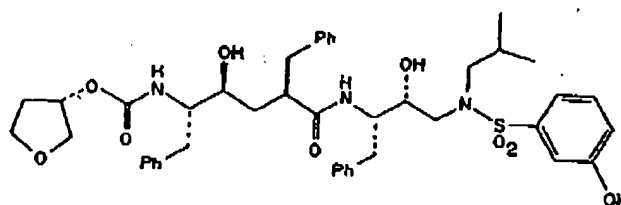
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CLAIMS AS PENDING

Claims as Pending

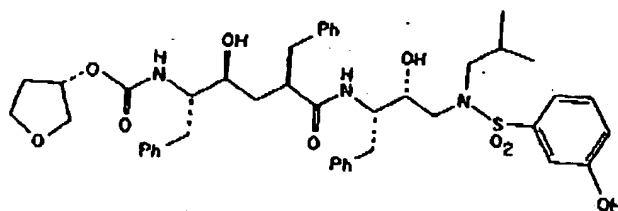
1. (twice amended) A polypeptide aspartic acid protease inhibitor comprising two or more transition-state isosteres in the polypeptide backbone, which have different orientations that mimic the transition state of the aspartic acid protease, and bind to different subsite binding pockets in the aspartic acid protease.
2. The inhibitor of claim 1 wherein the transition-state isostere is $-\text{CH}(\text{OH})-\text{CH}_2-$.
4. (Amended) The composition of claim 1 wherein the aspartic acid protease inhibitor is an HIV protease inhibitor.
5. The inhibitor of claim 1 which is UIC-98-056 having the following structure:



6. The inhibitor of claim 2 wherein the $\text{CH}(\text{OH})\text{-CH}_2$ is substituted with two other kinds of isosteres.
7. (Amended) A method for treating a patient infected with a pathogen expressing an aspartic acid protease comprising the oral administration of an aspartic acid protease inhibitor comprising two or more transition-state isosteres.
8. The method of claim 7 wherein the transition-state isostere is $\text{CH}(\text{OH})\text{-CH}_2\text{-}$.
10. (Amended) The method of claim 7 wherein the protease inhibitor inhibits HIV protease.

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11. The method of claim 10 wherein the inhibitor is UIC-98-056 having the following structure:



12. The method of claim 8 wherein the $\text{CH}(\text{OH})\text{-CH}_2$ is substituted with two other kinds of isosteres.

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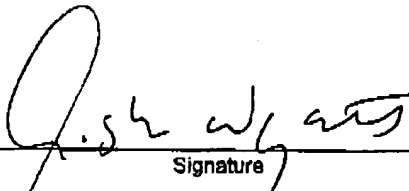
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